4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-N-0202]

Over-The-Counter Drug Monograph System--Past, Present, and Future; Public Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public hearing; request for comments.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is announcing a public hearing to obtain input on the Over-The-Counter (OTC) Drug Review (sometimes referred to as the OTC Monograph Process, OTC Monograph, or OTC Drug Review). The Agency would like input on how to improve or alter the current OTC Monograph Process for reviewing nonprescription drugs (sometimes referred to as OTC drugs) marketed under the OTC Drug Review. This public hearing is being held to obtain information and comments from the public on the strengths and weaknesses of the current OTC Monograph Process, and to obtain and discuss ideas about modifications or alternatives to this process.

DATES: Public Hearing: The public hearing will be held on March 25 and 26, 2014, from 9 a.m. to 4 p.m. The meeting may be extended or may end early depending on the level of public participation. Register to attend or provide oral testimony at the meeting by March 12, 2014. See REGISTRATION AND REQUEST TO PROVIDE ORAL TESTIMONY for information on how to register or make an oral presentation at the meeting. Written or electronic comments will be accepted until May 12, 2014.

ADDRESSES: The public hearing will be held at FDA's White Oak Campus, 10903 New Hampshire Ave., Bldg. 31, rm. 1503A, Silver Spring, MD, 20993-0002. Entrance for the public

meeting participants (non-FDA employees) is through Building 1 where routine security check procedures will be performed. For parking and security information, please refer to http://www.fda.gov/AboutFDA/WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm241740.htm.

FOR FURTHER INFORMATION CONTACT: Mary Gross, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20903-0002, 301-796-3519, FAX: 301-847-8753, mary.gross@fda.hhs.gov; or Georgiann Ienzi, Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Silver Spring, MD 20903-0002, 301-796-3515, FAX: 301-595-7910, georgiann.ienzi@fda.hhs.gov.

REGISTRATION AND REQUEST TO PROVIDE ORAL TESTIMONY: The public hearing is free and seating will be on a first-come, first-served basis. If you wish to attend the public hearing or make an oral presentation, see section IV of this notice (Attendance and/or Participation in the Public Hearing) for information on how to register and the deadline for registration. For those who cannot attend in person, information about how to access a live Webcast of the meeting will be located at: http://www.fda.gov/Drugs/NewsEvents/ucm380446.htm.

COMMENTS AND TRANSCRIPTS: Interested persons may submit either electronic comments regarding this document to http://www.regulations.gov or written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should annotate and organize your comments to identify the specific questions identified by the topic to which they refer. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets

Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at http://www.regulations.gov.

Transcripts of the hearing will be available for review at the Division of Dockets Management and at http://www.regulations.gov approximately 45 days after the hearing. A transcript also will be available in either hard copy or on CD-ROM after submission of a Freedom of Information request. Send requests to the Division of Freedom of Information (ELEM-1029), Office of Management Programs, Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857.

SUPPLEMENTARY INFORMATION:

FDA is announcing a public hearing to obtain input on the OTC Drug Review. We believe that the OTC Drug Review needs a critical examination at this juncture to examine whether and how to modernize its processes and regulatory framework. The Agency is interested in exploring ways to re-engineer the process of regulating OTC drugs that are currently regulated under the OTC Monograph Process to, among other things, create a process that is more efficient and more responsive to newly emerging information and evolving science, and to allow for more rapid product innovation where appropriate.

I. Background

FDA has been assessing the OTC Monograph Process and, in particular, has been considering how effectively the monograph system is functioning in today's world, 40 years after its inception, from the scientific, policy, and process perspectives. We are now soliciting opinions about whether and how to modernize the process for the future.

A. The Past: OTC Drug Review Implementation and Accomplishments

1. OTC Drug Review Regulatory Framework

FDA's regulations in 21 CFR part 330 describe the conditions for a drug to be considered generally recognized as safe and generally recognized as effective (GRAS/GRAE) and not misbranded. If a drug meets each of the conditions contained in part 330, as well as each of the conditions contained in any applicable OTC drug monograph, and other applicable regulations, it is considered GRAS/GRAE and not misbranded, and is not required by FDA to obtain approval of a new drug application (NDA) under section 505 of the FD&C Act (21 U.S.C. 355).

The lengthy notice and comment rulemaking procedures for evaluating each therapeutic category are set forth at § 330.10. These regulations require a three part regulatory rulemaking process including the publication of an Advanced Notice of Proposed Rulemaking, a Tentative Final Monograph (TFM) or Proposed Rule, and a Final Monograph or Final Rule to establish the conditions under which drugs under the OTC Drug Review are considered GRAS/GRAE and are not misbranded. FDA does not require OTC products conforming to the conditions of a final monograph and other applicable regulations to have approved NDAs prior to marketing. As a corollary, it has also generally been FDA's enforcement approach since the early days of the OTC Drug Review to not pursue regulatory action against OTC products marketed in conformance with the conditions proposed in a TFM. (See Compliance Policy Guide Section 450.200 Drugs--General Provisions and Administrative Procedures for Recognition as Safe and Effective at:

http://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074388.htm

).

2. Accomplishments of FDA's OTC Drug Review

The OTC Drug Review has been successful in a variety of ways. Under the OTC Drug Review, FDA was able to evaluate the safety and efficacy of thousands of OTC drug products by therapeutic category, instead of reviewing NDAs for each drug product. FDA has issued final monographs for the majority of the original drug categories (see 21 CFR parts 331 to 361) and over 150 TFMs. The final rules cover large segments of the OTC marketplace. Examples include fluoride toothpastes, acne products, and topical antifungals. As a result of the OTC Drug Review, thousands of OTC drugs that FDA determined are GRAS/GRAE and not misbranded are regulated under final monographs and continue to be available to consumers, and numerous other OTC drugs that were considered unsafe, ineffective, or both, have been removed from the market.

B. The Present: Challenges and Changed Landscapes

Our examination, however, has revealed significant challenges associated with the OTC Drug Review as it functions today. When we look at how rapidly science now evolves and the impact this has had on the emergence of drug safety issues and on drug development, it is clear to us that questions need to be asked about whether this impact necessitates a more agile and responsive process than the OTC Drug Review allows. When the OTC Monograph Process was initially established and implemented in the early 1970s, the multistep rulemaking strategy was thought to be an effective and efficient approach to reviewing large categories of active ingredients in drug products at the same time given what was the current thinking about the known science related to these ingredients. Indeed, the questions we are raising in this notice about the OTC Drug Review become all the more important to the public health when we compare the statutory changes that have been made to update the regulation of prescription NDA

drugs to address the scientific advances in evaluating drug safety. These changes give FDA the ability to quickly obtain new information and take administrative action as needed efficiently and effectively.

We have identified what we believe are the biggest challenges to efficiently and effectively regulating under the OTC Drug Review. We are also interested in feedback that identifies any other scientific or regulatory challenges associated with the OTC Drug Review that are not described here.

We believe that the biggest challenges of the current system are:

- the large number of products marketed under the OTC Drug Review for which there are not yet final monographs,
- limitations on FDA's ability to require, for example, new warnings or other labeling changes to address emerging safety or effectiveness issues for products marketed under the OTC Drug Review in a timely and effective manner, and
- the inability of the OTC Drug Review to easily accommodate innovative changes to products regulated under the OTC Drug Review.

1. Monographs That Have Not Been Finalized

The OTC Drug Review is one of the largest and most complex regulatory undertakings ever at FDA. It now consists of approximately 88 simultaneous rulemakings in 26 broad categories that encompass hundreds of thousands of OTC drug products marketed in the United States and some 800 active ingredients for over 1,400 different ingredient uses. However, several significant segments of the OTC marketplace are still not covered by final monographs, and these products may lack sufficient data for FDA to determine whether they are safe, effective, or both. Under the enforcement approach we have been using since the early days of the OTC Drug

Review, most of these products have remained on the market pending finalization of their monograph. Over the years, it has become clear that one unintended consequence of this enforcement approach is that it creates negative incentives for those who manufacture or market these OTC drugs to conduct studies or otherwise respond to safety concerns as to do so may hasten a determination that their product is not GRAS/GRAE.

2. Emerging Safety Concerns, Evolving Science, and Product Formulation

The OTC Monograph Process also presents challenges to FDA's ability to respond to emerging safety issues, keep pace with evolving science, and ensure the consistent safety and effectiveness of varying formulations.

a. New safety concerns can arise before or after a monograph is finalized. The OTC Drug Monograph Process is not agile enough to quickly change a monograph to address new safety concerns that may be identified during the rulemaking process or after a monograph is finalized (e.g., the addition of a warning into the monograph regulation, narrowing of an indication in the monograph regulation, or removal of an active ingredient from the monograph). Although the Agency may be able to take some actions to deal with safety issues that emerge, in order to change the monograph under the current process FDA engages in a lengthy rulemaking process. This process for changing a monograph is not well-adapted to address new safety issues with the speed and agility that are necessary to serve the public health.

b. Keeping Pace with Evolving Science. As we have already described, the OTC Drug Review is not able to easily keep pace with evolving science. When the OTC Drug Review was established, it was generally thought that safety and effectiveness evaluations for the various active ingredients would be fairly straightforward and would not necessarily need continuous reexamination over time. Forty years later we know that information and data regarding

medicine and science are changing at increasingly rapid rates. For example, scientific advancements have changed what is known about how drugs act in the body and in turn, how drugs are evaluated by FDA. These changes cannot be reflected under the OTC Drug Review in an efficient or timely manner. For example, many drug products regulated under the OTC Drug Review are indicated for use by children and are labeled with dosing instructions for this population. For most OTC monograph products, the information and data available at the time the initial advisory review panels established by FDA evaluated the various active ingredients, in the 1970s, lacked specific data on use in children and infants. FDA did what was scientifically customary at the time, and extrapolated known data to use in children by simply reducing adult doses by a percentage. For most monographs that include specific labeling for use in the pediatric population, the pediatric dosing instructions were developed in this manner. The science of pharmacokinetics has advanced over the years and, as a result, the preferred approach to pediatric dosing has changed. Ideally, data from actual use in the pediatric population would be needed for an indication for use in children.

In addition, with some categories of OTC drugs, changes in patterns of use take place which, in turn, impact consumer exposure to the drugs. Exposure patterns are a key component of any safety and effectiveness assessment. The current process of changing a monograph does not contain an efficient mechanism to assess or address these kinds of changes to exposure patterns.

c. Product Formulation. Under the OTC Drug Review, the monographs set forth the conditions under which a specific active ingredient used in a drug product is GRAS/GRAE and not misbranded. The monographs, however, generally do not dictate what other non-active ingredients can be added, or other aspects of the formulation (other than the general requirement

that they be safe and suitable and not interfere with the effectiveness of the preparation, see § 330.1(e)). Thus, under the OTC Drug Review, products in their final formulation are not specifically evaluated by the Agency to ensure product safety, effectiveness, and consistency. Although FDA regulations require that inactive ingredients not interfere with the safety or efficacy of the drug product, for drug products marketed under the OTC Drug Review, FDA generally does not receive information about specific varying formulations that it can use to ensure that the final finished drug products meet the standards for safety and effectiveness.

3. Limited Opportunity for Innovation

Eligibility for the OTC Drug Review is limited to active ingredients that were on the market in their specific dosage forms at the inception of the OTC Drug Review, and products that have become eligible under the Time and Extent Application process set forth at § 330.14. Thus, when manufacturers develop new combinations of ingredients or new dosage forms (e.g. dissolving films or tablets), the OTC Drug Review is not facile in accommodating these types of changes. Due to these changes, products that are not eligible for consideration under the OTC Drug Review would otherwise require an NDA prior to marketing.

II. The Future: Modernizing the OTC Drug Review

In light of the challenges posed by the OTC Drug Review, FDA believes it is time for considering ideas for modernizing the regulation of drugs under the OTC Drug Review. We are interested in hearing ideas for changes to the existing OTC Monograph Process or ideas for its replacement with an entirely new regulatory or statutory framework.

In developing suggestions for change, FDA notes that many of the OTC Drug Review's present day challenges are systemic, and thus cannot be addressed solely by increasing resources. In this section, we identify some preliminary ideas for potential changes to the OTC Monograph

Process. Although none of these ideas appear likely to lead to a comprehensive solution, we are sharing them as a starting point for a discussion on modernizing the OTC Drug Review. Our summary of these initial ideas here is not intended to define the limits of the kind of changes that might be proposed. We are interested in hearing a full range of ideas, including novel ideas for new regulatory frameworks.

Suggestions and other comments from the public need not be comprehensive to be useful. FDA is interested in ideas that may not solve every problem, but do address one or more of them. Ideally, a comprehensive solution (made up of a single proposal or a group of proposed solutions) would address all the challenges of the current system. We believe that an ideal, comprehensive solution would:

- use modern standards for safety and efficacy,
- provide an efficient mechanism for finalizing the status of drug products that are currently marketed under pending TFMs,
- allow for innovative changes to drug products,
- provide FDA with the ability to respond promptly to emerging safety or effectiveness concerns,
- allow FDA to easily and quickly require additional information or data necessary to develop pediatric labeling where appropriate, and
- allow FDA to obtain final formulation information about individual products or readily establish final formulation testing standards.

We recognize that the preliminary concepts we discuss in this document touch upon some, but not all, of the challenges we have identified. In addition, these ideas are not necessarily

limited to approaches for which FDA has existing statutory authority. These preliminary ideas are:

- identifying a streamlined process that would allow prompt resolution of existing TFMs,
- issuing monographs by administrative order,
- issuing regulations to require product specific information and expanding the use of guidances, and
- expanding the NDA deviation process.

We invite the public to comment on these potential options, but we also encourage comments that propose other ideas.

A. Promptly Resolve Existing Tentative Final Monographs Pursuant to a Streamlined Process

FDA is considering ways to more efficiently bring TFMs to closure. We are interested in ideas for developing streamlined processes under which the Agency could promptly finalize the existing TFMs.

B. Issue Monographs by Administrative Order

This idea would involve establishing a process similar to that enacted by the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144) for device reclassifications. FDASIA changed the process by which devices are reclassified under section 513(e) of the FD&C Act from notice and comment rulemaking to an administrative order process (see 21 U.S.C. 360c(e)(1)(A)(i)). Under this model, monographs could be established by administrative order, after issuance of a proposed order for comment.

C. Issuing Regulations to Require Product Specific Information and Expanding the Use of Guidances

FDA could issue new regulations that would require that manufacturers submit, prior to marketing, limited information about individual products that will be using active ingredients that have been determined to be GRAS/GRAE. The individual product information requested might be similar to, but less detailed than, what is required under an NDA and could include, for example, labeling, and quality and pharmacokinetic information. FDA could then issue guidances recommending the types of information FDA would be seeking. FDA's use of guidances under this framework could increase the Agency's flexibility to address specific product issues as they arise.

D. Expand the NDA Deviation Process

The OTC Drug Review regulations provide a process for approving a drug product that complies with the conditions of a final monograph except for a deviation (§ 330.11). In this instance, a sponsor can apply for an NDA deviation by submitting an NDA showing that the product complies with the conditions of the monograph except for the deviation and providing the necessary data to demonstrate the safety and effectiveness of the product with the deviation. For example, an OTC monograph may not cover certain dosage forms of a monograph ingredient. The manufacturer of a proposed different dosage form could submit an NDA that relies on the final monograph to demonstrate the safety and efficacy for the drug except for the differences related to the change in dosage form. The NDA would also need to include the appropriate data to demonstrate the safety and effectiveness of the new dosage form. The approved NDA would be specific only to the NDA sponsor and would not amend the monograph.

Industry has not utilized the NDA deviation process as a pathway to marketing very often. The Agency is interested in learning why this is and whether there are changes that could be made to the existing NDA deviation process that would make it a more attractive alternative for industry and that could allow marketing of additional drug products without having to submit a full NDA.

III. Scope of the Public Hearing

FDA is holding this public hearing to seek input on possible ways to modernize the OTC Monograph Process in order to make the process more responsive to emerging safety information and scientific advances. We would like feedback from a variety of interested members of the public, including consumers; industry; and pharmacists, physicians, and other members of the medical community. FDA is interested in obtaining information and public comment in the following areas:

A. Strengths and Weaknesses of the Existing OTC Drug Review

- What aspects of the OTC Drug Review continue to function effectively?
- Which aspects of the OTC Drug Review are most in need of change?
- Are there additional mechanisms to eligibility for the OTC Drug Review that could be explored? If so, what should be the parameters of eligibility?
- Why is the NDA deviation process rarely used by industry? Are there changes to that process that would make it a more appealing and appropriate alternative pathway?

B. Preliminary Concepts for Modernization Described in This Document

We welcome views on the following preliminary concepts identified by FDA for modernizing the OTC Drug Review:

- Ideas for a streamlined process that would allow us to promptly resolve all TFMs.

- Issue monographs by administrative order.
- Issue regulations to require product specific information and expand the use of guidances.
- Expand the NDA deviation process.

C. Your Suggestions for Modifications or Alternatives to the OTC Drug Review

- What alternatives or changes to the OTC Drug Review would modernize or improve FDA's regulation of monograph drugs?
- What changes can facilitate speedier finalization of the remaining monographs?
- How can the Agency most expeditiously address emerging safety issues for drugs regulated under the OTC Drug Review?
- Are there specific changes to the OTC Drug Review that the Agency could employ to address the lack of pediatric data for some final monographs?
- Should the only alternative to marketing an OTC drug under an OTC monograph be an NDA or abbreviated NDA approval? If not, what could another alternative be?
- Are there other regulatory mechanisms (not necessarily used for the regulation of drug products) that are used by other agencies in the United States or in other countries that FDA could consider using to regulate OTC drugs products?

IV. Attendance and/or Participation in the Public Hearing

The public hearing is free and seating will be on a first-come, first-served basis. If you wish to make an oral presentation during the hearing, you must register by submitting either an electronic or a written request by 5 p.m. on March 12, 2014, to Mary Gross or Georgiann Ienzi (see FOR FURTHER INFORMATION CONTACT). Submit electronic requests to CDEROTCMONOGRAPH@fda.hhs.gov. We recommend that you register early because

seating is limited. You must provide your name, title, business affiliation (if applicable), address, telephone and fax numbers, email address, and type of organization you represent (e.g., industry, consumer organization, etc.). You also should submit a brief summary of the presentation, including the discussion topic(s) that will be addressed and the approximate time requested for your presentation. FDA encourages individuals and organizations with common interests to coordinate and give a joint, consolidated presentation. Registrants will receive confirmation once they have been accepted to attend the meeting. FDA may limit both the number of participants from individual organizations and the total number of attendees based on space limitations. Registered presenters should check in before the hearing.

Participants should submit a copy of each presentation to Mary Gross or Georgiann Ienzi (see FOR FURTHER INFORMATION CONTACT) no later than 5 p.m. on March 12, 2014. We will file the hearing schedule, indicating the order of presentation and the time allotted to each person, with the Division of Dockets Management (see COMMENTS AND TRANSCRIPTS).FDA will post an agenda of the public hearing and other background material at least 3 days before the public hearing and additional information will be available at: http://www.fda.gov/Drugs/NewsEvents/ucm380446.htm (select this hearing from the events list).

We will mail, email, or telephone the schedule to each participant before the hearing. In anticipation of the hearing presentations moving ahead of schedule, participants are encouraged to arrive early to ensure their designated order of presentation. Participants who are not present when called risk forfeiting their scheduled time.

If you need special accommodations due to a disability, contact Mary Gross or Georgiann Ienzi (see FOR FURTHER INFORMATION CONTACT) at least 7 days in advance of the hearing.

V. Notice of Hearing Under 21 CFR Part 15

The Commissioner of Food and Drugs is announcing that the public hearing will be held in accordance with part 15 (21 CFR part 15). The hearing will be conducted by a presiding officer, who will be accompanied by FDA senior management from the Office of the Commissioner and the relevant centers.

Under § 15.30(f), the hearing is informal and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer and panel members may question any person during or at the conclusion of each presentation (§ 15.30(e)). Public hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (21 CFR part 10, subpart C) (§ 10.203(a)). Under § 10.205, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. The hearing will be transcribed as stipulated in § 15.30(b). (See section VII for more details.) To the extent that the conditions for the hearing as described in this document conflict with any provisions set out in part 15, this notice acts as a waiver of those provisions as specified in § 15.30(h).

Dated: February 19, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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